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Buprenorphine-Mediated Transition from Opioid Agonist to Antagonist Treatment: State of the Art and New Perspectives

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Abstract

Constant refinement of opioid dependence (OD) therapies is a condition to promote treatment access and delivery. Among other applications, the partial opioid agonist buprenorphine has been studied to improve evidence-based interventions for the transfer of patients from opioid agonist to antagonist medications. This paper summarizes PubMed-searched clinical investigations and conference papers on the transition from methadone maintenance to buprenorphine and from buprenorphine to naltrexone, discussing challenges and advances. The majority of the 26 studies we examined were uncontrolled investigations. Many small clinical trials have demonstrated the feasibility of in- or outpatient transfer to buprenorphine from low to moderate methadone doses (up to 60–70 mg). Results on the conversion from higher methadone doses, on the other hand, indicate significant withdrawal discomfort, and need for ancillary medications and inpatient treatment. Tapering high methadone doses before the transfer to buprenorphine is not without discomfort and the risk of relapse. The transition buprenorphine-naltrexone has been explored in several pilot studies, and a number of treatment methods to reduce withdrawal intensity warrant further investigation, including the co-administration of buprenorphine and naltrexone. Outpatient transfer protocols using buprenorphine, and direct comparisons with other modalities of transitioning from opioid agonist to antagonist medications are limited. Given its potential salience, the information gathered should be used in larger clinical trials on short and long-term outcomes of opioid agonist-antagonist transition treatments. Future studies should also test new pharmacological mechanisms to help reduce physical dependence, and identify individualized approaches, including the use of pharmacogenetics and long-acting opioid agonist and antagonist formulations.

Keywords

Drug addiction; evidence-based treatment; implant; injection; long-acting; extended release; low-dose; high-dose; methadone; naltrexone; partial agonist; dependence; tolerance; withdrawal; transfer; non-opioid; pharmacogenetics

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CONFLICT OF INTEREST

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INTRODUCTION

The treatment of opioid dependence (OD) has more pharmacotherapeutic options than other substance abuse disorders. Agonist medications, such as methadone or buprenorphine, are part of long or short-term therapies to break the abusing cycle. Antagonist medications and in particular naltrexone, accelerate the detoxification process and are prescribed post-detoxification to help prevent relapse. Recently, long-acting naltrexone and buprenorphine formulations have been introduced to improve compliance [1, 2]. Nonetheless, the path to recovery is often complex: individuals may engage in detoxification, opioid agonist or antagonist treatments multiple times. The transition between therapies is both a risk for relapse and an opportunity to improve outcomes, favoring treatment access and retention in continuing care [3–5].

Despite existing interventions, the large majority of OD individuals do not receive treatment and many fail to continue treatment following detoxification [6]. Increasing the efficiency of opioid antagonist therapies would enhance effective alternatives and help promote the availability of agonist maintenance treatments to new clients [7, 8].

Research and clinical efforts have focused on easing the transition from agonist to antagonist medications and the partial opioid agonist buprenorphine has been considered a promising pharmacological tool.

Transitional Pharmacological Properties of Buprenorphine

Buprenorphine displays ‘antagonist’ properties that may help decrease the level of physical dependence in the transfer from full opioid agonist to antagonist agents, and shows at the same time the ability to attenuate withdrawal symptoms through its agonist action. Several mechanisms may be involved:

1. Buprenorphine is a partial agonist at the μ opioid receptor (e.g. it has low intrinsic opioid activity). Most of the familiar opioid effects (e.g. pain reduction, feelings of reward and pleasure, and respiratory suppression) are less intense than those produced by heroin, morphine, or methadone [9]. This helps downplay the effects of a conversion from full agonist to antagonist agents [10];
2. Buprenorphine has high μ receptor affinity and slow association/dissociation kinetics. These properties moderate the process of methadone displacement and naltrexone occupation of the receptor, explaining the gradual onset, longer duration, and slow offset of buprenorphine’s effects [11, 12];
3. The action of buprenorphine at other receptors may help tone down motivational and behavioral aspects of dependence and withdrawal during a transition. Antagonism at κ-opioid and to lesser extent δ-opioid receptors reduces tolerance, dependence and attenuate the typical dysphoria that accompanies withdrawal [13, 14]. Concurrent agonism at the opioid receptor-like (ORL-1) receptor has been linked to attenuated drug-seeking and use in animal models [15];
4. Although most of buprenorphine’s neural and cellular mechanisms remain to be elucidated, its anticipated ability of ‘resetting’ the opioid receptor function activated by methadone [16] is now receiving explanation. For example, laboratory animal studies suggest that only buprenorphine among opioid agonist medications is able to block and reverse desensitization and internalization of the μ receptor induced by methadone or other full agonists [17], a mechanism that may contribute to the development of opioid tolerance and physical dependence [18].

The Transition from Methadone to Naltrexone Using Buprenorphine

There are multiple reasons for a conversion of methadone-treated patients to buprenorphine, before switching them to naltrexone [19]. The first explanation is pharmacological: buprenorphine's partial agonism leads to a reduced risk of overdose, and a longer duration of action permits less frequent dosing than methadone [9]. Secondly, the office-based treatment may be associated with less fear of stigma and better compatibility with social obligations, including work and study. Following a continuum of care, patients who improve may transition from receiving methadone in a structured opiate treatment program to receiving buprenorphine in a more flexible outpatient setting [20]. Finally, there may be medical reasons to the transfer. For instance, methadone use has been associated with ventricular arrhythmias, in particular with the variant described as "torsade de pointes" [21–23]. Similar complications have not been documented with buprenorphine and transitioning may be a safer alternative to some patients [24, 25].

About 10% of buprenorphine-treated patients have transferred from methadone (RE Johnson, personal communication, 2007), and 10 to 20% of patients in methadone maintenance chose the conversion, when given the option [26, 27]. The cost of buprenorphine treatment and a reduced availability at substance abuse programs that offer methadone maintenance may play a role in the decision [28, 29]. Considerable clinical concerns associated with the possibility of inducing significant withdrawal discomfort and attrition during the transfer limit the choice [9]. It is the responsibility of clinicians to carefully scrutinize the reasons of a conversion to buprenorphine and discuss with stable methadone maintained patients of the risk of failure and relapse [30].

On the other hand, the use of buprenorphine to stabilize OD patients before transitioning to naltrexone may result in a more efficient solution than a direct conversion from methadone and contribute to improving patient's compliance with antagonist maintenance treatment. In addition to pharmacological aspects, the office-based buprenorphine approach is usually structured to include routinary behavioral treatment and offers an opportunity to continue to engage patients in psychosocial aspects of relapse prevention, once they transfer to naltrexone. This approach may help identify an intermediate level of intervention between acute detoxification and long-term agonist maintenance of OD, further expanding therapeutic options. Moreover, induction to naltrexone from buprenorphine could become a more cost-effective detoxification intervention than a methadone-naltrexone sequence for those patients who cannot or do not intend to continue on long-term antagonist treatment [31, 32].

Thus, a review of the transitional use of buprenorphine may show potential to improve a range of evidence-based OD interventions. In this paper, we summarize the results of clinical investigations on the transfer from methadone maintenance through buprenorphine to naltrexone, discussing ongoing challenges and advances. While non-pharmacological interventions are indispensible to the treatment of drug dependence, the review has a more restricted focus on pharmacotherapy.

Literature Review Methods

We searched Pubmed/MEDLINE, EMBASE, The Cochrane Library, and the ISI Web of Knowledge[SM] Conference Proceedings Citation Index-Social Sciences & Humanities (CPCI-SSH) from database inception to August 2011. Search terms that were used individually or in combination included methadone, buprenorphine, naltrexone, transfer or transition, to identify clinical investigations on buprenorphine-mediated transfer of OD patients from methadone maintenance to naltrexone. To identify any articles missed by the electronic search, the bibliographies of the electronically identified articles were analyzed

and appropriate articles were retrieved, based on the title and abstract. Conference reports of clinical trials were included if results were available by hand searching, or were obtained from the authors upon request. Short-term observation following the transfer (less than 12 hours) was an exclusion criterion. Dose challenge studies and investigations that do not describe a transfer to full-dose naltrexone (50 mg), or offer naltrexone as a take-up treatment option were also excluded. We review here separate sets of investigations on the transfer from methadone to buprenorphine and from buprenorphine to naltrexone

CLINICAL INVESTIGATIONS ON THE TRANSITION FROM METHADONE MAINTENANCE TO BUPRENORPHINE (TABLE 1)

The substitution of buprenorphine for methadone can be more difficult than transitioning from heroin to buprenorphine, because the lasting effects of methadone require waiting longer before buprenorphine induction, in particular among patients in methadone maintenance treatment (MM) [33].

Transfer from Low Methadone Maintenance Dose (Up to 30 mg)

Lukas *et al.* [34] were the first to report on MM patients switching abruptly (e.g. without taper) to buprenorphine, and then discontinuing treatment. Subjective, behavioral and physiologic ratings (including EEG) were collected over two months. Buprenorphine induction caused mild opioid withdrawal, similar to what observed following its discontinuation. Probably due to the small sample (n=3), no significant differences were observed in the transfer from low versus moderate MM doses (25 mg *vs* 58 mg and 60 mg), though it was concluded that buprenorphine did not fully substitute for MM. Early outpatient transfer studies [16, 35] describe withdrawal ratings peaking in the initial 2 days of buprenorphine treatment and discomfort declining over 2 weeks. Opioid use and treatment retention in MM patients were comparable with those of patients who transferred from heroin. However, withdrawal intensity was more intense during the second week of buprenorphine treatment among MM patients, especially those receiving a lower buprenorphine dose [16]. Law *et al.* [36] used a comparable transfer modality among inner city addicts, who were returned to methadone after few days on buprenorphine without adverse effects.

Conversion to buprenorphine and taper during inpatient MM detoxification was associated with reduced withdrawal intensity, but comparable completion rates to detoxification using the alpha-2 adrenergic clonidine or the analgesic lefetamine [37]. An outpatient, slow detoxification study [38] showed the feasibility of switching patients to buprenorphine following MM taper to 30 mg, or abrupt conversion from a lower dose. A separate group of patients was transferred when feeling uncomfortable during taper and switched at methadone doses of about 30 mg. Patients on doses lower than 30 mg experienced significantly less discomfort in the transfer.

Transfer from Moderate Methadone Maintenance Dose (40–70 mg)

Levin *et al.* [39] tapered methadone from 60 to 30 mg over 4 days before transferring patients to buprenorphine, while Greenwald *et al.* [40] tapered the same dose of methadone to 45 mg in 1 day, reporting a shorter withdrawal duration (2 *vs* 3 days), with no ancillary medication use. The peak withdrawal intensity in the Greenwald study was recorded 6 or more hours after initial buprenorphine dose, suggesting that addition of ancillary treatment may be reasonable to control significant symptoms occurring outside the treatment setting. In a lofexidine-assisted abrupt discontinuation study, the duration of methadone therapy is insufficient to define a typical maintenance treatment. However, participants were clinically assessed and administered methadone stabilization doses for few days to match the severity

of their dependence condition. Patients receiving higher doses (50–70 mg) showed more intense withdrawal and required higher quantities of alpha-2 adrenergic medication (up to 2.4 mg/day) during transfer, compared to those on lower doses and a lower physical dependence condition [41].

Banys *et al.* [42] studied MM (up to 60 mg) patients, showing complete, partial, or insufficient relief of withdrawal symptoms in response to small, 'analgesic' doses of buprenorphine (0.15 mg–0.30 mg), independent of the methadone dose. Buprenorphine was administered at the onset of methadone withdrawal and repeated at regular intervals of 1, 3 or more hours, for 1 or more days.

Transfer from High Methadone Maintenance Dose (>70 mg)

In a retrospective study at a MM program [26], 13.4% of patients accepted to switch to buprenorphine, offered as an interim goal during slow, high dose MM (up to 155 mg) tapering that was unsuccessful. A similar investigation in an office-based buprenorphine treatment setting showed 24% of patients taking up on the transfer offer, though no one receiving MM 60 mg or higher accepted the conversion [27]. Clark *et al.* [43] abruptly discontinued MM among hospitalized patients, inducing buprenorphine after 2 or more days. Higher MM doses (up to 100 mg), a shorter time to buprenorphine induction and the female gender were associated with a more severe withdrawal. Commencing the induction with low (0.8 mg) or high dose (32 mg) buprenorphine resulted in better outcomes (less withdrawal discomfort and shorter duration of symptoms, respectively) than the ones observed with a 4 mg dose. Sixty percent of patients who completed the conversion were still taking buprenorphine after 3 months. Jones *et al.* [44] used the intermediate shorter acting full agonist immediate-release morphine to facilitate the transfer of MM pregnant OD patients to buprenorphine and noted that reduced withdrawal discomfort during morphine treatment was followed by worsening of symptoms and relapse in the first 3 days of buprenorphine treatment. Twenty-five per cent of patients completed the study. In the protocol by Urban and Sullivan [45], buprenorphine induction was a successful rescue treatment of acute opioid withdrawal discomfort precipitated by naltrexone in MM patients. Bouchez *et al.* [46] reported that outpatient administration of buprenorphine to patients on high MM dose required several days of clinical supervision and the use of ancillary medications, as opposed to uncomplicated transfer from lower MM doses. Finally, Rosado *et al.* [47] demonstrated that a high MM transition is more comfortable when buprenorphine induction dose is split and administered at time intervals. Twenty per cent of patients in their study showed little signs of withdrawal with any of the buprenorphine induction doses tested, though about 40% of participants did not complete the protocol.

Discussion

Current published clinical practice recommends reducing methadone to 30 mg/day for a minimum of 1 week and performing the transfer to buprenorphine not earlier than 24 hours after the last methadone dose [33, 48]. A series of relatively small clinical studies we examined show the transfer MM-buprenorphine is feasible over a range of low to moderate methadone doses (up to 60–70 mg), following abrupt discontinuation or taper, preferably assisted by ancillary treatment, with a 24-hour interval between medications. However, due to differences in design and individual variability, a single protocol cannot be formulated. Studies show that the need of ancillary medications and inpatient treatment increases at comparatively high methadone doses. It is rather common for patients in MM treatment to have high levels of physical dependence. About 70% of patients receive more than 60 mg per day of methadone in the USA [49, 50]. Lowering the dose of methadone and/or increasing the interval between the last dose of methadone and buprenorphine may be less acceptable in this case, as it exposes patients to relapse. There are few pilot studies on the

management of these doses and they offer preliminary evidence of alternative methods. Until larger clinical trials are completed, inpatient treatment and use of ancillary medications remain the mainstay approach for these patients, as recommended by the 'Physician Clinical Support System for Buprenorphine' [30].

CLINICAL INVESTIGATIONS ON THE TRANSITION FROM BUPRENORPHINE TO NALTREXONE (TABLE 2)

A transfer to naltrexone is considered safe for patients who are methadone-free for 10–14 days [51]. The application of rapid and ultra-rapid transition techniques to reduce the duration of transfer is labor-intensive and shows inconsistent results, associated in some cases with safety concerns [52, 53]. Chronic buprenorphine administration produces less physical dependence, as demonstrated by the occurrence of less severe withdrawal symptoms following its discontinuation and by the need of higher antagonist doses to precipitate withdrawal in buprenorphine than methadonetreated volunteers [54]. The transitional use of buprenorphine has been tested across treatments ranging from buprenorphine detoxification followed by naltrexone induction, to buprenorphine and naltrexone co-administration.

Buprenorphine Discontinuation and Naltrexone Administration

Following a switch of MM patients to buprenorphine for 1 month, Kosten *et al.* [55] abruptly discontinued the medication by blind substitution with placebo and followed up with infusion of the short-acting antagonist naloxone. Withdrawal was less intense than the one recorded in methadone patients receiving a similar treatment [56]. A few hours later naloxone-induced withdrawal had resolved and naltrexone administration was associated with minimal discomfort. Compared with high-dose intravenous naloxone, the administration of low dose oral naltrexone (1 mg) did not induce significant withdrawal in buprenorphine-treated OD patients [54]. Among patients who discontinued buprenorphine and were given naltrexone 1 mg titrated to full-dose, withdrawal was reported to be mild and naltrexone maintenance could be initiated in about half the sample, though only a small proportion was retained in treatment after 2 weeks [57]. Comparing different dose regimens and settings, patients who were hospitalized during transfer and received the initially high, withdrawal-inducing dose of opioid antagonist medication were more successful at continuing on naltrexone [16]. Kosten concluded: "When a transition to naltrexone is desired, better success and greater efficiency can be obtained by precipitating buprenorphine withdrawal" [58]. This rationale is not dissimilar from the one formulated for rapid and ultra-rapid detoxification approaches [53, 59], and may result in easier and safer transfer, though direct comparisons are limited. Collins *et al.* [60] randomized heroin abusers to single-dose buprenor-phine, ultra-rapid or clonidine-assisted detoxification, followed by naltrexone. Rates of naltrexone induction were higher following buprenorphine (97%) and ultra-rapid (94%) treatments, than with clonidine (21%), though differences in naltrexone retention became non-significant over 12 weeks (buprenorphine 24%, ultra-rapid 20%, clonidine 9%). Ultra-rapid detoxification showed a significantly higher rate of serious adverse events than the other treatments. In an outpatient study at a primary care program [61], buprenorphine tapering heroin abusers were as likely to receive a full dose naltrexone as patients treated with clonidine and naltrexone (both 81%), and more likely than those detoxified with clonidine alone (65%). However, retention in the 8-day treatment did not significantly differ across conditions (buprenorphine 60%, clonidine-naltrexone 54%, clonidine 65%). Sigmon *et al.* [62] performed outpatient naltrexone induction among buprenorphine-tapering prescription opioid abusers when urine levels of the medication were undetectable. About 43 % of participants were induced to naltrexone maintenance. Patients who completed buprenorphine taper without relapsing (33%) had higher rates of

naltrexone induction (100% *vs* 11%), 12-week treatment completion (60% *vs* 0%), and reduced opioid use (82.9% *vs* 2.4%) compared with those who relapsed during taper.

Buprenorphine and Naltrexone Co-Administration

Umbricht *et al.* [63] reported on the first clinical investigation of buprenorphine in combination with naltrexone. Heroin users adding naltrexone to a 4-day buprenorphine taper did not need significantly more ancillary medications than patients randomized to receiving naltrexone 4 days after buprenorphine discontinuation. The buprenorphine-naltrexone group showed non-significantly lower rates of full dose naltrexone induction (62.5% *vs* 78.6%), and 8-day treatment completion (56% *vs* 76%). Objective withdrawal was the only recorded measure of discomfort. Although peak withdrawal intensity after naltrexone was not significantly different between treatments and withdrawal duration was shorter in the buprenorphine-naltrexone group (3 *vs* 5 days), half of the total dropouts were recorded within 24 hours of the first naltrexone dose, contributing to a significantly reduced length of stay (5.9 days *vs* 7.4 days). Johnson [64] investigated the time needed to reach full naltrexone dose in a small sample of OD individuals tapering buprenorphine. One third received concurrently 2 mg daily increments of naltrexone, starting at 2 mg when buprenorphine was 8mg. All patients were scheduled to receive naltrexone at rapid dose increments (12.5 to 50 mg) over a 4-day period, following buprenorphine cessation. Earlier naltrexone use did not expedite naltrexone induction. Neither group successfully reached the full naltrexone dose until 9 days after buprenorphine discontinuation. Although the two groups did not differ significantly in their requirements of ancillary medications, withdrawal varied in duration and intensity by individual and not by treatment, ranging from 3 to 8 days. Only 17% of patients were taking naltrexone at 4 weeks, none of them had received buprenorphine/naltrexone induction. The author concluded: 'buprenorphine/naltrexone treatments should not be given concurrently'. In the inpatient study by Clark *et al.* [65], a small group of heroin abusers and buprenorphine-treated patients tapered buprenorphine in 2 to 4-days, combined with increasing doses of naltrexone. Following buprenorphine discontinuation, patients received naltrexone 50 mg and were discharged. Higher subjective withdrawal discomfort was reported in the initial 2 days of treatment. All patients completed the treatment protocol. Although only 33% of patients were still taking naltrexone after 4 weeks, overall opioid use was reduced by 50% or more, compared with admission to treatment. Gerra *et al.* [66] evaluated the outcome of naltrexone induction and maintenance treatment in heroin-dependent patients. The protocol consisted of a 4-day buprenorphine taper. Patients received very low-dose naloxone IV on day 2 and 3 and were administered naltrexone (10 mg) on day 4. From day 5 through the remainder of the study, patients were administered naltrexone 50 mg, or a naltrexone 50mg/buprenorphine 4 mg combination. All patients completed naltrexone induction and 56.7% of them were receiving treatment after 12 weeks. The use of naltrexone/buprenorphine was associated with significantly better retention in treatment (73% vs. 40%), reduced use of opioids (4.5% *vs* 25%) and cocaine (9.1% *vs* 33.3%), and improved mood symptoms and craving.

Discussion

Taken together, published clinical practice recommends induction to full dose naltrexone 5–7 days after buprenorphine discontinuation [48]. The studies we have reviewed here show the feasibility of transferring OD patients from buprenorphine to naltrexone in a shorter time, if an inpatient treatment option is available. With regard to the results of pilot investigations on naltrexone use in combination with buprenorphine, these are preliminary and not all in agreement. Larger clinical trials and outpatient investigations with adequate follow-up observation are needed.

Additionally, comparisons of different transfer methods were limited, including the use of alpha-2 adrenergic agonist agents, with or without early opioid antagonist administration. In some case, insufficient follow up of full naltrexone administration prevents from making meaningful comparisons [61, 63]. Other studies describe better early outcomes of buprenorphine *vs* clonidine-only induction [60]. Clonidine and lofexidine are effective in reducing a number of opioid withdrawal symptoms [67, 68], and participate in the regulation of reward and stress-related drug taking [69–71]. A recent investigation showed that the addition of a stimulant medication improved patient retention and reduced the incidence of hypotension during clonidine-mediated opioid detoxification and induction with naltrexone [72]. In another study, a lofexidine–naloxone combination was superior to methadone taper in favoring post-detoxification abstinence [73]. Future investigations should explore the efficacy of alpha-2 adrenergic agonists combinations with buprenorphine and naltrexone.

Further, a common finding of buprenorphine-naltrexone transition studies is the rather high rate of early naltrexone discontinuation: 60% or more patients terminated naltrexone in the 4 weeks following induction, not dissimilar to what observed in methadone-naltrexone transfer investigation [74]. The study by Gerra and collaborators [66] represents a significant exception, though it is insufficient to determine an association between method of transition and retention in treatment. Available evidence does not consistently link early drop-outs with the quality of discomfort experienced in the transition [75–77], and has not identified other significant factors beside an association of low naltrexone adherence with poor maintenance outcome [1, 78]. Further research on determinants of naltrexone retention is warranted to better elucidate the effectiveness of the interventions.

CHALLENGES AND ADVANCES

Regulation of OD Level

Current approaches to lowering the level of physical dependence and attenuate opioid withdrawal in the conversion from full opioid agonist to antagonist medications include agonist taper and delayed antagonist induction. The identification of several opioid and non-opioid mechanisms may offer future alternative treatment approaches. We briefly discuss some of them.

Opioid Regulation

- A rapid reduction of physical dependence and withdrawal duration with high dose buprenorphine administration in methadone treated patients or naloxone/naltrexone use in buprenorphine-treated individuals [16, 43, 45, 63] is labor-intensive and may not be well tolerated by some patients, impinging on acceptance of the new treatment. Some protocols have used low or very low, repeated doses of buprenorphine or naloxone/naltrexone in a stepwise fashion [42, 47, 65, 66]. This may partly explain high retention and low opioid use rates described in some studies of methadone-buprenorphine or buprenorphine-naltrexone transition [65, 66]. Indeed, repeated administration of very low dose opioid antagonists in combination with agonist medications attenuates opioid dependence and withdrawal in animal models [79, 80], and similar findings were observed in clinical studies [81, 82].
- Gerra *et al.* [66] tested a buprenorphine/naltrexone combination treatment, previously proposed by Rothman and co-workers [14] as a functional κ opioid receptor antagonist to control post-detoxification dysphoria. Buprenorphine shows strong κ and δ opioid receptor affinity that reinforces the weak antagonist action of naltrexone, associated with significant agonism at the nociceptin receptor (ORL-1). The mixed receptor activity of this combination may

attenuate not only dysphoric mood and opioid seeking behavior and use, but also cocaine and alcohol abuse [83].

- Opioid antagonist agents are antagonist also of the immune system's pattern recognition receptor, toll-like receptor (TLR) 4, has been associated with CNS glial activation and the development of opioid tolerance and physical dependence in animals [84]. Interestingly, (+)-naloxone and naltrexone isomers are active TRL 4 antagonists, while being inactive at the classic opioid receptors [85, 86]. If their clinical use proves to be safe following ongoing investigations, it may lead to reduce opioid dependence without interfering with μ receptor activity.

Non Opioid Regulation

- γ-aminobutyric acid (GABA)-glutamate imbalance, in particular enhanced glutamatergic transmission, is thought to play a role in the development and maintenance of OD [87]. The N-Methyl-D-Aspartate (NMDA)-glutamate receptor antagonist memantine has shown to block the development of OD and reduce withdrawal intensity in preclinical and clinical models [88, 89]. In a recent study, memantine did not improve the outcome of oral naltrexone treatment of OD [90], although it was added following naltrexone induction, when 25% of patients had already withdrawn from the study. Along this line, pure GABA receptor agonists such as baclofen, vigabatrin, tiagabine and gabapentin have shown efficacy as short-term adjunct treatment of OD and withdrawal in some controlled studies [91–95].
- Multiple interactions exist between opioid and cannabinoid systems in the development of physiological dependence [96]. Recent clinical investigations show that moderate cannabinoid agonism is linked to improved compliance with oral naltrexone treatment [97], while moderate opioid antagonism may in turn reduce cannabis use [98]. Modulation of cannabinoid neurotransmission during the transfer may contribute to regulate neurovegetative and dopaminergic activity that are altered during opioid withdrawal [99, 100], although any potential treatment would need careful clinical evaluation.

Medication Formulations and Bioavalability

A significant portion of the clinical investigations on buprenorphine have been conducted using a liquid sublingual preparation, and only a few transfer trials have adopted the combination buprenorphine/naloxone (Tables 1 and 2). The bioavailability of buprenorphine sublingual tablet is between 50% [101, 102] and 75% [103, 104] of an equivalent dose of liquid solution. Although the clinical effects of adding naloxone to the formulation have been considered negligible [105], bioavailability of the active medication from the buprenorphine/naloxone tablet seems higher than that of the buprenorphine tablet alone (respectively 90% and 60% of the solution) [106]. It is not entirely clear how such differences influence treatment efficacy [104], though it complicates the interpretation of research data. A buprenorphine sublingual film preparation was recently introduced showing reduced time and steadier rate of absorption compared with the tablet (data on file, Reckitt Benckiser Pharm Inc). Its use may contribute to sensibly decrease the individual variance in buprenorphine bioavailability. In addition, the investigation of slow-release buprenorphine has progressed from uncontrolled studies [107–110], to phase III clinical trials [111]. These formulations may help deliver the medication in a sustained but gradually declining manner over several days, eliminating the fluctuations in concentration associated with daily administrations.

Several slow-release naltrexone formulations have been tested to improve compliance with opioid antagonist treatment [1], and an extended release naltrexone injection was recently approved in the USA for the treatment of OD [112, 113]. Current guidelines suggest a similar approach for induction to oral and depot naltrexone treatment [114]. Future investigations should determine whether a short to long acting conversion and a transition between slow-release opioid agonist and antagonist agents carry significant clinical advantages and help improve long-term outcomes.

Heterogeneous Response

A search for the 'ideal' transitional approach cannot discount the investigation of individualized treatments. Several induction studies have shown wide variability in treatment response, even within a small sample. Low dose buprenorphine is well tolerated and effective in a minority of patients [42, 43, 47], while buprenorphine taper is associated with significant differences in clinical response, while using the same treatment approach [43, 62, 64]. Buprenorphine detoxification studies suggest the influence of type and severity of opioid use and racial/ethnic status on the outcome [115–117]. Transfer investigations using buprenorphine have tested individualized approaches based on dose flexibility [64], subjective withdrawal reports [36, 38, 41, 42, 46], or rate of buprenorphine elimination [62]. Attempts to match more homogeneous subgroups with effective pharmacotherapies could become easier once biologically defined endophenotypes are identified using pharmacogenetics. One example is offered by the alcohol dependence treatment, where ongoing efforts to identify biological endophenotypes for naltrexone and acamprosate may lead to preselect potential responders to treatment and include the study of polymorphisms of dopamine, glutamate and opioid receptors [118, 119]. The A118G polymorphism in the μ receptor has been suggested to contribute to individual variability in pain management and drug addiction [120–122]. Significant differences in reactivity to stress have been found among carriers of A118G receiving buprenorphine [123], and OD patients treated with naltrexone [124]. In addition, polymorphisms of genes coding for opioid-metabolizing enzymes and transporter proteins may affect outcomes by influencing dose requirements and tolerability [125, 126]. Clinical indications will benefit from including evaluation of functional genetic variants in large trials of buprenorphine and naltrexone treatment of OD.

CONCLUSION

Recent advances in the neurobiology of addiction may lead to develop new and more effective pharmacotherapies, however a major concern lies in promoting access to available treatments and improving their effectiveness. The antagonist treatment of OD has been for a long time associated with inconsistent results, but the availability of new long acting formulations and the therapeutic needs of a rapidly growing OD population justify renewed efforts [1]. Although the results of using buprenorphine as a transitional agent from opioid agonist to antagonist medications have been insufficient to modify current practices, the amount of information gathered can lead to test and expand effective pharmacotherapy alternatives, and facilitate access to existing treatments. Ultimately, our understanding of the therapeutic role of naltrexone in OD is likely to improve by comparing depot and oral formulations, as well as by matching the long-term ability of naltrexone and opioid agonist maintenance to reduce drug use and health costs, while improving patients' quality of life. Future large multicenter randomized clinical trials should compare sublingual buprenorphine with long-acting formulations and different transition modalities, evaluating their influence on the compliance with, and effectiveness of subsequent opioid antagonist treatments.

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REFERENCES

1. Mannelli P, Peindl KS, Wu LT. Pharmacological enhancement of naltrexone treatment for opioid dependence: a review. Subst Abuse Rehabil. 2011; 2011(2):113–123. [PubMed: 21731898]
2. O'Connor PG. Advances in the treatment of opioid dependence: continued progress and ongoing challenges. JAMA. 2010; 304(14):1612–1614. [PubMed: 20940391]
3. Kresina TF. Medication assisted treatment of drug abuse and dependence: global availability and utilization. Recent Pat Antiinfect Drug Discov. 2007; 2(1):79–86. [PubMed: 18221165]
4. McKay JR, Carise D, Dennis ML, et al. Extending the benefits of addiction treatment: practical strategies for continuing care and recovery. J Subst Abuse Treat. 2009; 36(2):127–130. [PubMed: 19161893]
5. Schaefer J, Cronkite R, Hu K. Differential relationships between continuity of care practices, engagement in continuing care, and abstinence among subgroups of patients with substance use and psychiatric disorders. Journal for Studies on Alcohol and Drugs. 2011; 72(4):611–621.
6. Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Publication No. SMA 10-4856. Summary of National Findings. Rockville: 2010.
7. Mark TL, Dilonardo JD, Chalk M, Coffey R. Factors associated with the receipt of treatment following detoxification. J Subst Abuse Treat. 2003; 24(4):299–304. [PubMed: 12867203]
8. Peterson J, Schwartz R, Mitchell S, et al. Why don't out-oftreatment individuals enter methadone treatment programmes? Int J Drug Policy. 2010; 21(1):36–42. [PubMed: 18805686]
9. Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. Drug Alcohol Depend. 2003; 70(2 Suppl):S59–S77. [PubMed: 12738351]
10. Bickel WK, Amass L. Buprenorphine treatment of opioid dependence: a review. Experimental Clinical Psychopharmacology. 1995; 3:477–489.
11. Tzschentke TM. Behavioral pharmacology of buprenorphine, with a focus on preclinical models of reward and addiction. Psychopharmacology (Berl). 2002; 161(1):1–16. [PubMed: 11967625]
12. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994; 55(5):569–580. [PubMed: 8181201]
13. Richards ML, Sadee W. *In vivo* opiate receptor binding of oripavines to mu, delta and kappa sites in rat brain as determined by an ex vivo labeling method. Eur J Pharmacol. 1985; 114(3):343–353. [PubMed: 2998812]
14. Rothman RB, Gorelick DA, Heishman SJ, et al. An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. J Subst Abuse Treat. 2000; 18(3):277–281. [PubMed: 10742642]
15. Ciccocioppo R, Economidou D, Rimondini R, Sommer W, Massi M, Heilig M. Buprenorphine reduces alcohol drinking through activation of the nociceptin/orphanin FQ-NOP receptor system. Biol Psychiatry. 2007; 61(1):4–12. [PubMed: 16533497]
16. Kosten TR, Morgan C, Kleber HD. Phase II clinical trials of buprenorphine: detoxification and induction onto naltrexone. NIDA Res Monogr. 1992; 121:101–119. [PubMed: 1406906]
17. Virk MS, Arttamangkul S, Birdsong WT, Williams JT. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. J Neurosci. 2009; 29(22):7341–7348. [PubMed: 19494155]
18. Koch T, Hollt V. Role of receptor internalization in opioid tolerance and dependence. Pharmacol Ther. 2008; 117(2):199–206. [PubMed: 18076994]

19. Fishman MJ, Wu LT, Woody GE. Buprenorphine for prescription opioid addiction in a patient with depression and alcohol dependence. Am J Psychiatry. 2011; 168(7):675–679. [PubMed: 21724673]
20. Whitley SD, Kunins HV, Arnsten JH, Gourevitch MN. Colocating buprenorphine with methadone maintenance and outpatient chemical dependency services. J Subst Abuse Treat. 2007; 33(1):85–90. [PubMed: 17588493]
21. Ehret GB, Desmeules JA, Broers B. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. Expert Opin Drug Saf. 2007; 6(3):289–303. [PubMed: 17480178]
22. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of druginduced QT prolongation and torsade de pointes. Am Heart J. 2007; 153(6):891–899. [PubMed: 17540188]
23. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005; 95(7):915–918. [PubMed: 15781034]
24. Fanoe S, Hvidt C, Ege P, Jensen GB. Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. Heart. 2007; 93(9):1051–1055. [PubMed: 17344330]
25. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007; 167(22):2469–2475. [PubMed: 18071169]
26. Calsyn DA, Malcy JA, Saxon AJ. Slow tapering from methadone maintenance in a program encouraging indefinite maintenance. J Subst Abuse Treat. 2006; 30(2):159–163. [PubMed: 16490679]
27. Salsitz EA, Joseph H, Frank B, et al. Methadone medical maintenance (MMM): treating chronic opioid dependence in private medical practice--a summary report (1983–1998). Mt Sinai J Med. 2000; 67(5–6):388–397. [PubMed: 11064489]
28. Knudsen HK, Ducharme LJ, Roman PM. Early adoption of buprenorphine in substance abuse treatment centers: data from the private and public sectors. J Subst Abuse Treat. 2006; 30(4):363–373. [PubMed: 16716852]
29. Saxon AJ, McCarty D. Challenges in the adoption of new pharmacotherapeutics for addiction to alcohol and other drugs. Pharmacol Ther. 2005; 108(1):119–128. [PubMed: 16055196]
30. Casadonte PP. Treatment Protocols, TIP #40: Patients dependent on long-acting opioids: Transfer from methadone to buprenorphine. PCSS-B Training: An Educational Resource for Those Treating Patients with Opioid Dependence. 2006
31. Gowing LR, Ali RL. The place of detoxification in treatment of opioid dependence. Current Opinions in Psychiatry. 2006; 19(3):266–270.
32. Stine SM, Kosten TR. Use of drug combinations in treatment of opioid withdrawal. J Clin Psychopharmacol. 1992; 12(3):203–209. [PubMed: 1629388]
33. Center for Substance Abuse Treatment. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction.
34. Lukas SE, Jasinski DR, Johnson RE. Electroencephalographic and behavioral correlates of buprenorphine administration. Clin Pharmacol Ther. 1984; 36(1):127–132. [PubMed: 6734042]
35. Kosten TR, Kleber HD. Buprenorphine detoxification from opioid dependence: a pilot study. Life Sci. 1988; 42(6):635–641. [PubMed: 3276999]
36. Law FD, Bailey JE, Allen DS, et al. The feasibility of abrupt methadone-buprenorphine transfer in British opiate addicts in an outpatient setting. Addiction Biology. 1997; 2:191–200.
37. Janiri L, Mannelli P, Persico AM, Serretti A, Tempesta E. Opiate detoxification of methadone maintenance patients using lefetamine, clonidine and buprenorphine. Drug Alcohol Depend. 1994; 36(2):139–145. [PubMed: 7851281]

38. Breen CL, Harris SJ, Lintzeris N, et al. Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. Drug Alcohol Depend. 2003; 71(1):49–55. [PubMed: 12821205]
39. Levin FR, Fischman MW, Connerney I, Foltin RW. A protocol to switch high-dose, methadone-maintained subjects to buprenorphine. Am J Addict. 1997; 6(2):105–116. [PubMed: 9134072]
40. Greenwald MK, Schuh KJ, Stine SM. Transferring methadonemaintained outpatients to the buprenorphine sublingual tablet: a preliminary study. Am J Addict. 2003; 12(4):365–374. [PubMed: 14504028]
41. Glasper A, Reed LJ, de Wet CJ, Gossop M, Bearn J. Induction of patients with moderately severe methadone dependence onto buprenorphine. Addict Biol. 2005; 10(2):149–155. [PubMed: 16191667]
42. Banys P, Clark HW, Tusel DJ, et al. An open trial of low dose buprenorphine in treating methadone withdrawal. J Subst Abuse Treat. 1994; 11(1):9–15. [PubMed: 8201637]
43. Clark, N.; Lintzeris, N.; Jolley, D. Transferring from high doses of methadone to buprenorphine: a randomised trial of three different buprenorphine schedules. College for Problems on Drug Dependence. Scottsdale, Arizona: 2006.
44. Jones HE, Suess P, Jasinski DR, Johnson RE. Transferring methadone-stabilized pregnant patients to buprenorphine using an immediate release morphine transition: an open-label exploratory study. Am J Addict. 2006; 15(1):61–70. [PubMed: 16449094]
45. Urban V, Sullivan R. Buprenorphine rescue from naltrexoneinduced opioid withdrawal during relatively rapid detoxification from high-dose methadone: a novel approach. Psychiatry (Edgmont). 2008; 5(4):56–58. [PubMed: 19727311]
46. Bouchez J, Beauverie P, Touzeau D. Substitution with buprenorphine in methadone- and morphine sulfate-dependent patients. Preliminary results. Eur Addict Res. 1998; 4(Suppl 1):8–12. [PubMed: 9767200]
47. Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100mg of daily methadone. Drug Alcohol Depend. 2007; 90(2–3):261–269. [PubMed: 17517480]
48. Lintzeris, N.; Clark, N.; Winstock, A., et al. National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence: abbreviated version. National Expert Advisory Committee on Illicit Drugs (NEACID) editor. Australia: Commonwealth Department of Health and Ageing; 2006.
49. D'Aunno T, Pollack HA. Changes in methadone treatment practices: results from a national panel study, 1988–2000. JAMA. 2002; 288(7):850–856. [PubMed: 12186602]
50. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev. 2003; (3):CD002208. [PubMed: 12917925]
51. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.
52. Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev. 2010; (1):CD002022. [PubMed: 20091529]
53. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA. 1998; 279(3):229–234. [PubMed: 9438745]
54. Kosten TR, Krystal JH, Charney DS, Price LH, Morgan CH, Kleber HD. Opioid antagonist challenges in buprenorphine maintained patients. Drug Alcohol Depend. 1990; 25(1):73–78. [PubMed: 2323312]
55. Kosten TR, Krystal JH, Charney DS, Price LH, Morgan CH, Kleber HD. Rapid detoxification from opioid dependence. Am J Psychiatry. 1989; 146(10):1349. [PubMed: 2675644]
56. Charney DS, Redmond DE Jr, Galloway MP, et al. Naltrexone precipitated opiate withdrawal in methadone addicted human subjects: evidence for noradrenergic hyperactivity. Life Sci. 1984; 35(12):1263–1272. [PubMed: 6482651]
57. Kosten TR, Morgan C, Kleber HD. Treatment of heroin addicts using buprenorphine. Am J Drug Alcohol Abuse. 1991; 17(2):119–128. [PubMed: 1862786]

58. Kosten TR. Buprenorphine for Opioid Detoxification: A Brief Review. Addictive Disorders & Their Treatment. 2003; 2(4):107–112.
59. Farrell M, Strang J. Compressed opiate withdrawal syndrome and naltrexone. Journal of Psychopharmacology. 1995; 9(4):383–385. [PubMed: 22298405]
60. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted *vs* buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. JAMA. 2005; 294(8):903–913. [PubMed: 16118380]
61. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, Rounsaville BJ. Three methods of opioid detoxification in a primary care setting. A randomized trial. Ann Intern Med. 1997; 127(7):526–530. [PubMed: 9313020]
62. Sigmon SC, Dunn KE, Badger GJ, Heil SH, Higgins ST. Brief buprenorphine detoxification for the treatment of prescription opioid dependence: a pilot study. Addict Behav. 2009; 34(3):304–311. [PubMed: 19081679]
63. Umbricht A, Montoya ID, Hoover DR, Demuth KL, Chiang CT, Preston KL. Naltrexone shortened opioid detoxification with buprenorphine. Drug Alcohol Depend. 1999; 56(3):181–190. [PubMed: 10529020]
64. Johnson RE. Buprenorphine: clinical use from maintenance to special populations. Research and Clnical Forums. 2001; 23(1):25–41.
65. Clark, N.; Lintzeris, N.; Bell, J. Accelerated opioid withdrawal with buprenorphine and naltrexone. Conference of the Australasian Professional Society on Alcohol and Other Drugs; Melbourne, Australia. 2005.
66. Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. J Psychopharmacol. 2006; 20(6):806–814. [PubMed: 16401652]
67. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev. 2009; (4):CD002021. [PubMed: 19821290]
68. Yu E, Miotto K, Akerele E, et al. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. Drug Alcohol Depend. 2008; 97(1–2):158–168. [PubMed: 18508207]
69. Dawe S, Gray JA. Craving and drug reward: a comparison of methadone and clonidine in detoxifying opiate addicts. Drug and Alcohol Dependence. 1995; 39(3):207–212. [PubMed: 8556969]
70. Samini M, Kardan A, Mehr SE. Alpha-2 agonists decrease expression of morphine-induced conditioned place preference. Pharmacol Biochem Behav. 2008; 88(4):403–406. [PubMed: 17945338]
71. Sinha R, Kimmerling A, Doebrick C, Kosten TR. Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. Psychopharmacology (Berl). 2007; 190(4):569–574. [PubMed: 17136399]
72. Ockert DM, Volpicelli JR, Baier AR Jr, Coons EE, Fingesten A. A nonopioid procedure for outpatient opioid detoxification. J Addict Med. 2011; 5(2):110–114. [PubMed: 21769056]
73. McCambridge J, Gossop M, Beswick T, et al. In-patient detoxification procedures, treatment retention, and post-treatment opiate use: comparison of lofexidine + naloxone, lofexidine + placebo, and methadone. Drug Alcohol Depend. 2007; 88(1):91–95. [PubMed: 17064857]
74. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. Addiction. 2006; 101(4):491–503. [PubMed: 16548929]
75. Kleber HD, Kosten TR. Naltrexone induction: psychologic and pharmacologic strategies. J Clin Psychiatry. 1984; 45(9 Pt 2):29–38. [PubMed: 6469934]
76. Krupitsky, E.; Zvartau, E.; Wood, G. Long-Acting Implantable Formulation of Naltrexone for Heroin Dependence: Results of Interim Analysis of Efficacy and Safety. Rockville, MD: NIDA International Program; 2009.
77. Tennant FS Jr, Rawson RA, Cohen AJ, Mann A. Clinical experience with naltrexone in suburban opioid addicts. J Clin Psychiatry. 1984; 45(9 Pt 2):42–45. [PubMed: 6469935]
78. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011; (4):CD001333.

79. Mannelli P, Gottheil E, Peoples JF, Oropeza VC, Van Bockstaele EJ. Chronic very low dose naltrexone administration attenuates opioid withdrawal expression. Biol Psychiatry. 2004; 56(4): 261–268. [PubMed: 15312814]
80. Powell KJ, Abul-Husn NS, Jhamandas A, Olmstead MC, Beninger RJ, Jhamandas K. Paradoxical effects of the opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. J Pharmacol Exp Ther. 2002; 300(2):588–596. [PubMed: 11805221]
81. Mannelli P, Patkar AA, Peindl K, Gorelick DA, Wu LT, Gottheil E. Very low dose naltrexone addition in opioid detoxification: a randomized, controlled trial. Addict Biol. 2009; 14(2):204–213. [PubMed: 18715283]
82. Mannelli P, Patkar AA, Peindl K, Gottheil E, Wu LT, Gorelick DA. Early outcomes following low dose naltrexone enhancement of opioid detoxification. Am J Addict. 2009; 18(2):109–116. [PubMed: 19283561]
83. McCann DJ. Potential of buprenorphine/naltrexone in treating polydrug addiction and co-occurring psychiatric disorders. Clin Pharmacol Ther. 2008; 83(4):627–630. [PubMed: 18212797]
84. Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, Watkins LR. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. ScientificWorldJournal. 2007; 7:98–111. [PubMed: 17982582]
85. Hutchinson MR, Zhang Y, Brown K, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Eur J Neurosci. 2008; 28(1): 20–29. [PubMed: 18662331]
86. Hutchinson MR, Zhang Y, Shridhar M, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun. 2010; 24(1):83–95. [PubMed: 19679181]
87. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. Bioessays. 2010; 32(9):748–755. [PubMed: 20730946]
88. Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW. The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. Psychopharmacology (Berl). 2001; 157(1):1–10. [PubMed: 11512037]
89. Popik P, Skolnick P. The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence. Pharmacol Biochem Behav. 1996; 53(4):791–797. [PubMed: 8801580]
90. Bisaga A, Sullivan MA, Cheng WY, et al. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend. 2011
91. Akhondzadeh S, Ahmadi-Abhari SA, Assadi SM, Shabestari OL, Kashani AR, Farzanehgan ZM. Double-blind randomized controlled trial of baclofen *vs* clonidine in the treatment of opiates withdrawal. J Clin Pharm Ther. 2000; 25(5):347–353. [PubMed: 11123486]
92. Assadi SM, Radgoodarzi R, Ahmadi-Abhari SA. Baclofen for maintenance treatment of opioid dependence: a randomized double-blind placebo-controlled clinical trial [ISRCTN32121581]. BMC Psychiatry. 2003; 3:16. [PubMed: 14624703]
93. Gonzalez G, Sevarino K, Sofuoglu M, et al. Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study. Addiction. 2003; 98(11):1625–1632. [PubMed: 14616189]
94. Kheirabadi GR, Ranjkesh M, Maracy MR, Salehi M. Effect of addon gabapentin on opioid withdrawal symptoms in opium-dependent patients. Addiction. 2008; 103(9):1495–1499. [PubMed: 18783503]
95. Rodriguez-Arias M, Aguilar MA, Manzanedo C, Minarro J. Preclinical evidence of new opioid modulators for the treatment of addiction. Expert Opin Investig Drugs. 2010; 19(8):977–994.
96. Robledo P, Berrendero F, Ozaita A, Maldonado R. Advances in the field of cannabinoid--opioid cross-talk. Addict Biol. 2008; 13(2):213–224. [PubMed: 18482431]
97. Raby WN, Carpenter KM, Rothenberg J, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict. 2009; 18(4):301–308. [PubMed: 19444734]
98. Mannelli P, Peindl K, Patkar AA, Wu LT, Pae CU, Gorelick DA. Reduced cannabis use after low-dose naltrexone addition to opioid detoxification. J Clin Psychopharmacol. 2010; 30(4):476–478. [PubMed: 20631574]

99. Muntoni AL, Pillolla G, Melis M, Perra S, Gessa GL, Pistis M. Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. Eur J Neurosci. 2006; 23(9):2385–2394. [PubMed: 16706846]

100. Pfizer T, Niederhoffer N, Szabo B. Search for an endogenous cannabinoid-mediated effect in the sympathetic nervous system. Naunyn Schmiedeberg Archives of Pharmacology. 2005; 371:9–17.

101. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol. 1999; 39(6):619–623. [PubMed: 10354966]

102. Schuh KJ, Johanson CE. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. Drug Alcohol Depend. 1999; 56(1):55–60. [PubMed: 10462093]

103. Chawarski MC, Moody DE, Pakes J, O'Connor PG, Schottenfeld RS. Buprenorphine tablet versus liquid: a clinical trial comparing plasma levels, efficacy, and symptoms. J Subst Abuse Treat. 2005; 29(4):307–312. [PubMed: 16311183]

104. Compton P, Ling W, Moody D, Chiang N. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. Drug Alcohol Depend. 2006; 82(1):25–31. [PubMed: 16144748]

105. Ciraulo DA, Hitzemann RJ, Somoza E, et al. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. J Clin Pharmacol. 2006; 46(2):179–192. [PubMed: 16432270]

106. Strain EC, Moody DE, Stoller KB, Walsh SL, Bigelow GE. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. Drug Alcohol Depend. 2004; 74(1):37–43. [PubMed: 15072805]

107. Lanier RK, Umbricht A, Harrison JA, Nuwayser ES, Bigelow GE. Evaluation of a transdermal buprenorphine formulation in opioid detoxification. Addiction. 2007; 102(10):1648–1656. [PubMed: 17854341]

108. Lanier RK, Umbricht A, Harrison JA, Nuwayser ES, Bigelow GE. Opioid detoxification *via* single 7-day application of a buprenorphine transdermal patch: an open-label evaluation. Psychopharmacology (Berl). 2008; 198(2):149–158. [PubMed: 18327673]

109. Sigmon SC, Moody DE, Nuwayser ES, Bigelow GE. An injection depot formulation of buprenorphine: extended bio-delivery and effects. Addiction. 2006; 101(3):420–432. [PubMed: 16499515]

110. Sigmon SC, Wong CJ, Chausmer AL, Liebson IA, Bigelow GE. Evaluation of an injection depot formulation of buprenorphine: placebo comparison. Addiction. 2004; 99(11):1439–1449. [PubMed: 15500597]

111. Ling W, Jacobs P, Hillhouse M, et al. From research to the real world: buprenorphine in the decade of the Clinical Trials Network. J Subst Abuse Treat. 2010; 38(Suppl 1):S53–S60. [PubMed: 20307796]

112. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. Ann N Y Acad Sci. 2011; 1216:144–166. [PubMed: 21272018]

113. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011; 377(9776):1506–1513. [PubMed: 21529928]

114. Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone Depot Formulations for Opioid and Alcohol Dependence: A Systematic Review. CNS Neurosci Ther. 2010

115. Brown ES, Tirado C, Minhajuddin A, et al. Association of race and ethnicity with withdrawal symptoms, attrition, opioid use, and side-effects during buprenorphine therapy. J Ethn Subst Abuse. 2010; 9(2):106–114. [PubMed: 20509084]

116. Whitley SD, Sohler NL, Kunins HV, et al. Factors associated with complicated buprenorphine inductions. J Subst Abuse Treat. 2010; 39(1):51–57. [PubMed: 20682186]

117. Ziedonis DM, Amass L, Steinberg M, et al. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. Drug Alcohol Depend. 2009; 99(1–3):28–36. [PubMed: 18805656]

118. Mann K, Hermann D. Individualised treatment in alcoholdependent patients. Eur Arch Psychiatry Clin Neurosci. 2010; 260(Suppl 2):S116–S120. [PubMed: 20953618]

119. Ooteman W, Naassila M, Koeter MW, et al. Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using genetic indicators. Addict Biol. 2009; 14(3):328–337. [PubMed: 19523047]

120. Deb I, Chakraborty J, Gangopadhyay PK, Choudhury SR, Das S. Single-nucleotide polymorphism (A118G) in exon 1 of OPRM1 gene causes alteration in downstream signaling by mu-opioid receptor and may contribute to the genetic risk for addiction. J Neurochem. 2010; 112(2):486–496. [PubMed: 19891732]

121. Mague SD, Blendy JA. OPRM1 SNP (A118G): involvement in disease development, treatment response, and animal models. Drug Alcohol Depend. 2010; 108(3):172–182. [PubMed: 20074870]

122. Walter C, Lotsch J. Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. Pain. 2009; 146(3):270–275. [PubMed: 19683391]

123. Kakko J, von Wachenfeldt J, Svanborg KD, Lidstrom J, Barr CS, Heilig M. Mood and neuroendocrine response to a chemical stressor, metyrapone, in buprenorphine-maintained heroin dependence. Biol Psychiatry. 2008; 63(2):172–177. [PubMed: 17850768]

124. Hyman SM, Hong KI, Chaplin TM, et al. A stress-coping profile of opioid dependent individuals entering naltrexone treatment: a comparison with healthy controls. Psychol Addict Behav. 2009; 23(4):613–619. [PubMed: 20025367]

125. Fonseca F, de la Torre R, Diaz L, et al. Contribution of cytochrome P450 and ABCB1 genetic variability on methadone pharmacokinetics, dose requirements, and response. PLoS One. 2011; 6(5):e19527. [PubMed: 21589866]

126. Li Y, Kantelip JP, Gerritsen-van Schieveen P, Davani S. Interindividual variability of methadone response: impact of genetic polymorphism. Mol Diagn Ther. 2008; 12(2):109–124. [PubMed: 18422375]

Key Learning Objectives

This paper presents an overview of the current available options to help the transfer from opioid agonist medications to antagonist treatment using the partial agonist buprenorphine. Key learning objectives include understanding pharmacological modalities of use and the benefits from using a partial opioid antagonist as a transitional agent, including relevant strengths and weaknesses.

Future Research Questions

What pharmacotherapy and biological approach work best in facilitating the transition to antagonist treatment in opioid addicted individuals? Are there new medications and interventions that work to reduce physical dependence on an individual basis and may favor long term outcomes, including the use of pharmacological combinations, new long-acting formulations and pharmacogenetic investigations?

Table 1

Clinical Investigations on the Transfer from Methadone Maintenance to Buprenorphine

Study	Description	Modality of transfer	Results
Randomized			
Janiri *et al.* 1994 [37] Inpatient RCT	M taper, transfer to Bup, clonidine, or lefetamine and detoxification. Physiologic, subjective, objective ratings, 9 days.	Taper M 15–35 to D1–3: 10 mg (n=13/39) 24-hour interval D4–7: Bup IM 0.9 mg tapered off	82% completed study, no treatment differences. Bup group showed milder withdrawal.
Breen *et al.* 2003 [38] Outpatient OL	M taper and transfer: 1) M 30mg, 2) when uncomfortable, 3) M < 30 mg. Subjective and objective ratings, urine test. Slow Bup taper for up to 16 weeks.	D1: 1) (n=19), 2) (n=19), 3) (n=17,control) 24-hour interval D2–5: Bup Tab 4mg →24 mg Ancillary medications	93% completed transfer, 69% completed Bup taper. 31% opioid-free at 4 weeks follow up. Transfer below M 30 mg = less discomfort.
Clark *et al.* 2006 [43] Inpatient OL	Abrupt transfer. Physiologic, behavioral and subjective ratings for 7 days.	D1: M 40–100 mg.(n=30) 48-hour or longer interval D2/3–8: Bup Tab 0.8mg, 4mg, 32 mg →32 mg Ancillary medications	90% completed study. 60% on Bup at 12 weeks. Lower M and Bup dose = less discomfort, higher Bup dose = shorter withdrawal duration.
Rosado *et al.* 2007 [47] Inpatient double-blind triple dummy	Abrupt transfer. Physiologic, subjective, objective ratings for several hours after each Bup dose, multiple 2-day sessions	D1: M 100 mg (n=16) 24-hour interval D2: Bup/Nal Tab 4,8,16, or 32 mg single/split	62.5% completed study. 18.7% no withdrawal with any Bup dose. 43.8% showed reduced discomfort with split dose.
Nonrandomized			
Lukas *et al.* 1984 [34] Inpatient Double-blind Double-dummy	Abrupt transfer. Physiologic and subjective ratings, 67 days.	D1–2: M25 mg, 58mg, 60 mg (n=1each) 24-hour interval D3–46: Bup 2mg SC	All completed transfer. Two completed study. Mild withdrawal, lasting several days. No differences associated with M dose.
Kosten *et al.* 1988, 92 [35,16] Outpatient OL	Abrupt transfer. Physiologic, objective ratings and urine test, 30 days.	D1: M 25 mg (n=14), Heroin (n= 27) 24-hour interval D2: Bup SOL 2–8 mg. D3–30 Bup 2–6 mg	71% completed study week1–4= 33%–19% opioid use Mild withdrawal lasting 2 weeks. Transferring from M and low Bup dose = more discomfort
Banys *et al.* 1994 [42] Inpatient OL	Abrupt transfer when uncomfortable. Subjective and objective ratings, 2–3 days.	D1:M 35–60 mg (n=15) 26–31-hour interval D2/3: Bup SOL 0,15 mg hourly, to 0.30 mg every 3 or more hours	Responders (n=6): withdrawal subsided. Partial responders (n=4): brief, partial relief. Non-responders (n=5): no relief. No differences associated with M dose.
Law *et al.* 1997 [36] Outpatient OL	Abrupt transfer when uncomfortable. Physiologic, subjective, objective ratings,4 days.	D1: M 20–30 mg (n=13) 24–26-hour interval D2–4: Bup SOL/Tab 4mg (n=2/11)	85% completed study. Mild increase of withdrawal on days 2–3. 77% preferred Bup to M.
Levin *et al.* 1997 [39] Inpatient Double-blind Double-dummy	M taper and transfer. Physiologic, subjective ratings, 14 days.	D1–4: M 60 mg (n=18) → 30mg 24-hour interval D5–6: Bup SOL 4mg → 8mg Ancillary medications	83% completed study. Withdrawal returned to baseline in 4 days.
Bouchez *et al.*	Abrupt transfer.	D1: M 40–90 mg (n=10)	All completed transfer.

Study	Description	Modality of transfer	Results
1998 [46] Outpatient OL	Subjective ratings for few days.	12–72-hour interval D2/3on: Bup Tab 2–16mg Ancillary medications	M >60mg = longer withdrawal (>3 days). Longer interval prior to induction and higher doses of Bup = less discomfort.
Greenwald *et al.* 2003 [40] Outpatient Double-blind Double-dummy	M taper and transfer. Physiologic, subjective ratings and self-reported opioid use for 10 days. Three-week Bup detoxification.	Day1: M 60 mg (n=5) → 45 mg 24-hour interval Day 2–8 Bup Tab 8 mg → 16 mg	All completed the study. Withdrawal discomfort increased for 2 days. Opioid use during the study was similar to baseline
Glasper *et al.* 2005 [41] Inpatient OL	M taper and transfer when uncomfortable. Physiologic, subjective and objective ratings collected for 8 days.	D4: M 30–49 mg (n=10), M 50–79 mg. (n=11) Tapered to half-dose 24-hour interval or longer D5–8: Bup Tab 4mg → 16 mg. Lofexidine	91% completed study. No group-differences.The higher dose group had more lofexidine (0–2.4 mg) and showed increased discomfort.
Jones *et al.* 2006 [44] Outpatient OL	Transfer M-immediate release Morphine- Bup in pregnant women. Physiologic, subjective ratings and fetal monitoring, 13 days.	D3–7: M 50–85 mg (n=4)→morphine 24-hour interval D8–13: Bup Tab 4mg →28 mg Ancillary medications	One patient completed the study. Withdrawal decreased during morphine treatment and increased with initial Bup doses. 25% relapsed (1/4)
Retrospective			
Calsyn *et al.* 2006 [26] Outpatient	Slow M taper, transfer to Bup offered as interim treatment. Several months duration.	Taper M 40–90 mg to D1: 17–24 mg (n=4) 24-hour interval D2–4: Bup Tab 6–12mg	13.3% (4/30) accepted Bup and completed transfer. One completed Bup taper. No patient completed M taper
Urban and Sullivan 2008 [45] Inpatient	Abrupt transfer M-naltrexone and Bup rescue. Physiologic, subjective and objective ratings for 7 days.	D1: M 70–130 mg (n= 5) 24-hour interval D2: Naltrexone 25 mg 30/45-minute interval D2: Bup/nal Tab 4–6 mg → individual dose Adjuvant clonidine	All completed/liked the transfer and later tapered Bup over several days
Salsitz *et al.* 2010 [27] Outpatient	Option of M taper and Bup transfer offered in office-based setting. Subjective and objective ratings for few days.	Individual taper to M 30–40 mg (n=25) 48–72-hour interval D2/4–7: Bup/Nal Tab 2–4 mg → individual	24% (25/104) attempted and completed transfer. The M dose of those who accepted Bup was 38.6 mg vs 53 mg of those who did not.

Abbreviations: Bup.=buprenorphine, D =day, IM= intramuscular, M= methadone, Nal= naloxone, OL= open label, RCT= randomized, controlled trial, SC= subcutaneous, SOL=sublingual solution, Tab= sublingual table

Table 2

Clinical Investigations on the Transfer from Buprenorphine to Naltrexone

Study	Method of NTX Induction	%NTX 50 mg	%NTX at Follow Up (Week)
NTX Administration Following Bup Discontinuation			
Kosten 1989 [55] Inpatient OL	D1–2: Bup 3mg SOL (n=5) →D3: placebo 24-hour interval D4: Nal 0.5 mg/kg IV×20 min, 5-hour interval D4–6: NTX12.5 mg→ 50 mg (*Nal protocol*)	100	40 (4)
Kosten 1991 [57] Inpatient OL	D1–2: Bup 2–6 mg SOL (n=28) → D3: placebo 24-hour interval D4–5: NTX 1 mg → 6 mg 24-hour interval D6: NTX 50 mg (*NTX protocol*)	71	10 (2)
Kosten 1992 [16] Inpatient/outpatient OL	*Nal protocol* (n=5) *NTX protocol* (n=13) Inpatient vs outpatient (n=18 vs 10)	100 84 89 vs 0	60 (2), 40 (4) 0.8 (2) 10 vs 0 (1)
O'Connor 1997 [61] Outpatient OL, randomized	D1–3: Bup 3mg SOL (n=53) 24-hour interval D4–5: NTX 25 mg → 50mg Adjuvant clonidine	81	N/A
Umbricht 1999 [63] Inpatient RCT	D1–4: Bup Tab 12→2 mg (n=28) D5–7: placebo D8: NTX 50 mg Ancillary medications	75	N/A
Johnson 2001 [64] Inpatient Single-blind Flexible dosing	D1–7: Bup Tab 12→2 mg (n=4) 24-hour interval D8–11(plan)-16 (completed): NTX 12.5 mg → 50 mg Ancillary medications	100	25 (4)
Collins 2005 [60] Inpatient OL, randomized	D1: Bup 8 mg Tab (n=37) 24–36-hour interval D3–6: 12.5 mg → 50 mg Ancillary medications	73	37.5 (4), 24 (12)
Sigmon 2009 [62] Outpatient OL flexible dosing	Bup/Nal Tab 4–16mg →0 mg (n= 15) D2–3: placebo D4–7: NTX 12.5 mg → 50 mg Ancillary medications	43	20 (12)
Naltrexone Administration During Bup Taper			
Umbricht 1999 [63] Inpatient RCT	D1–4: Bup Tab 12–2 mg (n=32) D2–8: NTX 12.5 mg → 50 mg Ancillary medications	62.5%	N/A
Johnson 2001 [64] Inpatient Single-blind Flexible dosing	D1–7: Bup Tab 12–2 mg day 1–5 (n=2) D3–11(plan)-16 (completed): NTX 2 mg → 50 mg Ancillary medications	100	0 (4)
Clark 2005 [65] Inpatient OL	D1–4: Bup Tab 4–8 → 2mg (n=6) D1–5: NTX 12.5 mg → 50mg Ancillary medications	100%	33 (4)
Gerra 2006 [66] Outpatient OL	D1–4: Bup/Nal Tab 8–4 mg (n=30 *) D2–3: Nal 0.04 mg IV ×10 /day D4–5: NTX 10 mg → 50 mg Ancillary medications	100%	90 (4), 40 (12)

* Only patients receiving naltrexone maintenance treatment alone were included (see text).

Abbreviations: Bup.= buprenorphine, D =day, IV= intravenous, M= methadone, Nal=naloxone, NTX= naltrexone, OL= open label, RCT= randomized, controlled trial, SC= subcutaneous, SOL= sublingual solution, Tab= sublingual tablets.